CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

# SUMMARY OF TOXICOLOGY DATA
# SILVER THIOSULPHATE

Chemical Code # 2856, Tolerance # 51562

Original: December 2, 2002

## I. DATA GAP STATUS

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| Chronic toxicity, rat: | Data gap, no study submitted.[1] |
| Chronic toxicity, dog: | Data gap, no study submitted.[1] |
| Oncogenicity, rat: | Data gap, no study submitted.[1] |
| Oncogenicity, mouse: | Data gap, no study submitted.[1] |
| Reproduction, rat: | No data gap, acceptable study, no adverse effect |
| Teratology, rat: | No data gap, acceptable study, possible adverse effect |
| Teratology, rabbit: | Data gap, no study submitted.[1] |
| Gene mutation: | No data gap, acceptable study, possible adverse effect |
| Chromosome effects: | No data gap, acceptable study, no adverse effect |
| DNA damage: | No Data gap, acceptable study, no adverse effect |
| Neurotoxicity: | Not required at this time |

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Toxicology one-liners are attached.

All record numbers through 019 201258 were examined.

** indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T195087
Original: M. Silva, 12/2/02

[1]This new active ingredient was submitted as a biochemical and these studies are not required at this time.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

No study submitted.

### CHRONIC TOXICITY, RAT

No study submitted.

### CHRONIC TOXICITY, DOG

No study submitted.

### ONCOGENICITY, RAT

No study submitted

### ONCOGENICITY, MOUSE

No study submitted

### REPRODUCTION, RAT

** 51562 - 013 187693 “Oral two-generation reproduction study with Florissant 100 in rats,” (Wolterbeek, Ir A.P.M., TNO Nutrition and Food Research, Zeist, The Netherlands; TNO Project #: 010.41219; TNO Study #: 3280; TNO Report #: v 3280; 1/21/02). Florissant 100 (90 - 101% pure) was administered by gavage to Wistar outbred (Crl:(WI)WU BR) rats (28/sex/dose) at 0 (tap water), 20, 200 and 1000 mg/kg for two successive generations (F0 & F1) through F2 weaning. Systemic NOEL = 200 mg/kg (F1 females had a statistically significant decrease in body weights, on occasion, during gestation at $\geq$ 200 mg/kg and in body weight gains at 1000 mg/kg. There was a statistically significant decrease in F1 maternal body weights during lactation at 1000 mg/kg. F1 female absolute body weights were statistically significantly decreased at termination at 1000 mg/kg. There were sporadic statistically significant decreases in food consumption in F1 females during premating and gestation at 1000 mg/kg.) Reproductive NOEL = 1000 mg/kg (There was a statistically significant decrease in females that were pregnant and males that sired at 20 mg/kg in the F0 parental generation which resulted in decreased female fecundity and female and male fertility indices. F0 males had statistically significantly decreased absolute and relative testes and epididymal weights at 20 mg/kg. There was an increase in testicular and epididymal pathology at 20 mg/kg in both F0 and F1 adult males. These effects appear to be incidental in the absence of any dose response. However, since they are greater than historical controls in many cases, they have been noted.) Pup NOEL > 1000 mg/kg (There were

no treatment-related effects at any dose.) **Acceptable. No adverse effect**. M. Silva, 9/19/02

## TERATOLOGY, RAT

**** 51562 - 014 187694** "Oral embryotoxicity/Teratogenicity Study with Florissant 100 in Rats," (Wolterbeek, Ir A.P.M.; TNO Study #: V3281; Project #: 010.41220; TNO Nutrition and Food Research, Zeist, The Netherlands; 5/28/01). Florissant 100 (90 - 101% pure) was administered by gavage to mated female Wistar outbred (Crl:(WI)WU BR) rats (28/dose) at 0 (tap water), 20, 200 and 1000 mg/kg (limit test) during gestation days 6 - 20. Maternal NOEL > 1000 mg/kg (There were no treatment-related effects at any dose.) Developmental NOEL = 200 mg/kg (There was a statistically significant increase in fetal incidence of pericardium filled with hemorrhagic fluid at 1000 mg/kg. Incidence in 1 - 5 digits incompletely ossified for both fetal and litter, were increased at 1000 mg/kg. Incidence in 1 - 5 digits incompletely ossified for fetuses were increased at $\geq$ 200 mg/kg and for litters at 1000 mg/kg, were increased.) This study is **acceptable** with **possible adverse fetal effects** (delayed ossification in digits and increased incidence in pericardium filled with hemorrhagic fluid). M. Silva, 9/16/02

## TERATOLOGY, RABBIT

No study submitted.

## GENE MUTATION

** 51562 - 016 187696 "Examination of Silver Thiosulfate in the Ames-test," (van Delft, J.H.M. and Blijleven, W.G.H.,TNO Nutrition and Food Research, Zeist, The Netherlands; Project #: 450064-016; TNO Report #: V95.716; 12/95). Silver thiosulfate (18.0 g/l $AgNo_3$. 200 g; $Na_2S_2O_3/5H_2O$, 50 g/l $Na_2S_2O_5$ in $H_2O$; 268 g salts/l $H_2O$) was used on *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at: Test 1: 0, 54, 163, 489, 1466 and 4399 ug/plate (+/- S9 metabolic activation) , Test 2: 0, 0.06, 0.18, 0.54, 1.63, 4.89, 14.7 and 44.0 ug/plate (no S9), Test 2: 0, 5.4, 16.3, 48.9, 147 and 440 ug/plate (+S9), Test 3: 0, 0.2, 0.6, 1.7, 5.0, 10 and 15 ug/plate (no S9) and Test 3: 0, 6.2, 18.5, 55.6, 166.7 and 500 ug/plate (+S9). All tests were performed on 3 plates/strain/dose. Toxicity was observed at 54 - 4399 ug/plate (no S9) and at $\geq$ 489 ug/plate (+S9). In Tests 2 & 3, toxicity was observed at 14.7 ug/plate (no S9) and at 440 ug/test (+S9). In Tests 4 & 5 toxicity occurred at 10 and/or 15 ug/plate (no S9) and at 500 ug/plate (+S9). There was no increase in gene mutation with treatment. The S9 mix was sterile and the positive controls functioned as expected (NOTE: E. coli WP2 uvrA strain was not included). **Acceptable**. M. Silva, 10/8/02.

**** 51562 - 016 187697** "Gene Mutation Test at the TK-Locus of L5178Y Cells with Silver Thiosulphate," (van Delft, J.H.M.; TNO Nutrition and Food Research, Zeist, The Netherlands; TNO Report #: V 95.715; Project #: 450041-002; 12/95). Florissant 100 (silver thiosulphate, 268 mg/ml in $H_2O$ consisting of: 18.0 g/l $AgNO_3$, 200 g/l $Na_2S_2O_3.5H_2O$, 50 g/l $Na_2S_2O_5$) was used on mouse lymphoma L5178Y cells at Test 1: 0 (culture media, no serum), 0 (DMSO), 0.01, 0.033, 0.1, 0.25, 0.5, 1, 2, 3, 4, 5 mg/ml (+S9 metabolic activation); Test 2: (culture media, no serum), 0 (DMSO), 0.01, 0.1, 0.5, 1, 2, 3, 4 mg/ml (no S9) and 0.01, 0.1, 0.5, 1, 2, 4, 5 mg/ml (+S9) for 4 hours at 37 °C to induce mutations at the TK-locus (duplicate cultures). The maximum concentration without S9 was 4 mg/ml and with S9 was 5 mg/ml, based on toxicity. The high concentrations were based on 70-90% cytotoxicity, as indicated by relative initial cloning efficiency. There was a significant increase in mutant frequency without S9 in Test 1 at 4 and 5 mg/ml and in Test 2 at 2, 3 and 4 mg/ml. With S9 there was a significant increase in mutant frequency in Test 1 at 2 and 4 mg/ml and in Test 2 at 0.1, 2, 4 and 5 mg/ml. The STS induced more small mutants than large mutants. The positive controls functioned as expected. **Possible adverse effect. Acceptable**. M. Silva, 10/11/02.

## CHROMOSOME EFFECTS

** 51562 - 016 187698 "Chromosome Aberration Test With Silver Thiosulphate in Cultured Chinese Hamster Ovary Cells," (van Delft, J.H.M. and de Vogel, N.; TNO Report #: V 95.767; TNO Nutrition and Food Research, Zeist, The Netherlands; 12/95). Florissant 100 (silver thiosulphate; 268 mg/ml in $H_2O$ consisting of: 18.0 g/l $AgNO_3$, 200 g/l $Na_2S_2O_3.5H_2O$, 50 g/l $Na_2S_2O_5$) was used on Chinese hamster ovary cells at Test 1: 0, 1, 5, 12.5, 25, 50, 75, 100, 150, 200, 300, 400, 500, 750, 1000, 3000 and 5000 ug/ml (with and without S9 metabolic activation) and Test 2: 0, 5, 12.5, 25, 50, 75, 100, 150, 175, 200 ug/ml (no S9) and 100, 200, 300, 400, 500, 750, 1000 and 2000 ug/ml (with S9). Tests without S9 had both 18 and 32 hour treatment and harvest times and tests with S9 had 3 hour treatment with 18 and 32 hour harvest times in Test 2. For each culture 1000 cells for mitosis and 200 cells (100/culture) for metaphase were evaluated. There were no treatment-related chromosomal aberrations induced in either test. **No adverse effect. Acceptable**. M. Silva, 10/15/02

## DNA DAMAGE

** 51562 - 016 187699 "Unscheduled DNA-Synthesis Test With Florissant 100 in Rat Liver Cells *in vivo*," (Krul, C.A.M., TNO Nutrition and Food Research, Zeist, The Netherlands, TNO Project #: 010.41239; TNO Study #: 3428; TNO Report #: V3428, 12/3/01. Florissant 100 (silver thiosulphate, 11 g silver/liter) was administered by gavage to Wistar outbred Crl:(WI) WU BR rats (6 males/dose; 2 males/dose for 2-AAF & DMN positive controls) at 0, 1000 and 2000 mg/kg. After 1-4 and 12-18 hours after treatment, the males were terminated and hepatocyte cultures were initiated. Hepatocyte cultures were incubated 18 hours, then cells were evaluated for unscheduled DNA synthesis by autoradiography. There were no treatment-related effects on body weights. Hepatocyte viabilities were acceptable and there were no clinical signs after animals were treated. Results showed no treatment-related DNA-repair activities in hepatocytes at either the first sacrifice time (2 - 4 hours) or the second sacrifice time (12 - 16 hours). The positive controls functioned as expected. **No adverse effect. Acceptable**. M. Silva, 10/16/02.

## NEUROTOXICITY

Not required at this time.

## MISCELLANEOUS STUDIES

(Oral)

51562 - 012 187692 "Sub-chronic (13-week) oral toxicity study with "silver-thiosulphate" in rats," (Arts, Ir J.H.E.; TNO Nutrition and Food Research, Zeist, The Netherlands; Project #: 40956; TNO Report #: V3343; 4/11/01). Silver thiosulphate (composed of $AgNO_3$ = 100%, $Na_2S_2O_3 + 5H_2O$ > 99.5%, $Na_2S_2O_5$ ~ 96 - 98%) was administered by oral gavage to Wistar outbred Crl:(WI)WU BR rats (10/sex/dose) at 0 (water), 20, 200 and 1000 mg/kg for 91 (males) or 92 (females) days. NOEL = 20 mg/kg (In males there was a statistically significant decrease in urine volume and pH and an increase in urine density at $\geq$ 200 mg/kg (day 87-88). There was a statistically significant increase in pigment deposits in cecum, colon, kidneys, liver, stomach and small intestines of both sexes at $\geq$ 200 mg/kg.) No adverse effect. **Acceptable**. M. Silva, 10/4/02

51562 - 019 201258 "Repeated Dose (90-Day) Oral Toxicity Study With Florissant 100 in Beagle Dogs," (Wijnands, M.V.W.; TNO Nutrition and Food Research, Zeist, The Netherlands; TNO Report #:

V3578; TNO Project #: 42041; TNO Study #: 3578; 7/02). Florissant 100 (silver thiosulphate, purity not stated, 11 g silver/l) was fed in diet to Beagle dogs (4/sex/dose) at 0, 35, 140 and 560 mg/kg for 90 days. Nominal NOEL = 35 mg/kg (Diarrhea occurred uniformly across groups, although it was slightly higher in high dose females, based on detailed weekly clinical observations (4/4 at 560 mg/kg versus 2/4 at 0 & 34 mg/kg and 1/4 at 140 mg/kg). High dose male #D32 showed hunched posture, sluggishness and salivation on Day 30. Mid-dose male #C20 had clinical problems Day 78 (severe diarrhea, tremors, salivation, loss of appetite) and was found dead Day 79. Several hematology parameters were affected (monocytes, albumin, MCH, neutrophils (%; dose-related), lymphocyte (%), monocytes, HB, PCV, MCV, cholesterol, ALP) at Day 42 and at termination in both sexes at $\geq$ 140 mg/kg. Several sites (adrenals, cecum, colon, duodenum, gall bladder, ileum, jejunum, liver, mesenteric lymph nodes, pancreas, rectum, stomach) had increased pigment deposits at $\geq$ 140 mg/kg. Males have statistically significantly decreased absolute liver weights at $\geq$ 140 mg/kg. Females had statistically significantly decreased absolute spleen weights at all doses. Females have statistically significantly decreased absolute heart weights at $\geq$ 140 mg/kg.) **No adverse effects. Not acceptable but possibly upgradeable** with submission of test article purity and test diet analysis. M. Silva, 10/21/02.

(Dermal)

**51562 - 011 187691** "Repeated Dose (28-Day) Dermal Toxicity Study with Silverthiosulphate in Rats," (Prinsen, M.K.; TNO Project #: 40954; TNO assay #s: 2258 (rangefinding study) & 2259 (28-day study); 4/00). Florissant 100 (aqueous silver thiosulphate; 50% treatment concentration) was administered dermally (semi-occluded) to Wistar outbred (Crl:(WI)WU BR) rats (5/sex/dose) at 0 (water), 100, 300 and 1000 mg/kg (6 hour/day, 5 days/week) for 4 weeks. Dermal NOEL < 100 mg/kg (There was skin pathology at all doses in females and at $\geq$ 300 mg/kg in males (parakeratosis, epidermal hyperplasia). Both sexes at 1000 mg/kg had skin pathology (epidermal ulcers, mixed inflammatory cell infilteration, spongiosis). There was an increase in yellow staining (by STS) at the treatment site, that was dose related in both sexes.) Systemic NOEL = 300 mg/kg (There was a statistically significant increase in neutrophils in females at 1000 mg/kg. Males, at $\geq$ 300 mg/kg, had slight, but statistically significantly increased Na. Females at 1000 mg/kg had statistically significantly increased ALP and decreased A/G ratio and creatine. At $\geq$ 300 mg/kg females had increased TP.) **Possible adverse effects** (Skin pathology was observed at all doses, especially in females. Although these pathologies were statistically significantly increased, the differences were not large.). **Unacceptable and not upgradeable** (no ophthalmology, limited histopathology). M. Silva, 9/25/02

Metabolism:

51562 - 015 187695 "Oral Absorption of Silver Thiosulfate in Rats," (Sparreboom-van Asperen, J.; TNO Nutrition and Food Research, Zeist, The Netherlands; TNO Project #: 010.45027; TNO Study #: 3598; TNO Report #: V 3598; 12/19/01). Florissant 100 was administered daily by gavage for 14 consecutive days to Wistar Crl:(WI) WU BR rats (4/sex/dose/group/timepoint) at Group A (Low Dose): 20 mg/kg (10 ml/kg bwt of 0.2% w/w Florissant 100 in $H_2O$) and Group B (High Dose): 200 mg/kg (10 ml/kg bwt of 2.0% w/w Florissant 100 in $H_2O$) with blood sampling time points at Day 0 (t = 0, 0.5, 1, 2, 4, 8, 12, 24) and Day 14 (t = 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 96). Control was from blood samples at t = 0. Conclusions: Silver was absorbed at a moderate rate after oral gavage treatment. Repeated treatment at 0.02 and 0.2 ml/kg of Florissant 100 resulted in a substantial accumulation of silver in both sexes, in spite of the oral bioavailability (estimated at < 0.5%). This was not a FIFRA Guideline study, therefore data are **supplemental**. **No adverse effect indicated**. M. Silva, 10/8/02.